Life Sciences Enterprise
DuPont Pharmaceuticals Company

October 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: Docket No. 99D-2635
Draft Guidance for Industry on ANDA's; Blend Uniformity Analysis
Notice of Availability and Request for Comments

Dear Sir/Madam:

We believe that the August 1999 draft Guidance on ANDA Blend Uniformity Analysis and its associated assay and RSD do not have scientific justification, are not reflective of industry practice, and do not improve the "quality" of the final product. Taking blend uniformity samples during process validation has been an accepted practice and GMP requirement for many years in the pharmaceutical industry. The purpose of process validation is to demonstrate, via sampling and extensive testing, that manufacturing processes are in control. These data are reviewed by FDA investigators during pre-approval and routine GMP inspections. Taking blend uniformity samples for every batch will not add value, and will unnecessarily burden QC labs throughout the pharmaceutical industry. In fact, performing blend uniformity analysis testing on every batch invalidates the concept of process validation.

The FDA's May 1987 Guideline of General Principles of Process Validation states: "Successfully validating a process may reduce the dependence upon intensive in-process and finished product testing." The routine collection of blend uniformity samples, subsequent to process validation studies and ANDA approval, is not current industry practice and has not been demonstrated via valid, scientific studies to increase assurance of uniformity in the finished dosage form unit. If the FDA is aware of such studies, references should be cited in the draft guidance. We do note that FDA "intends to seek the support of the Product Quality Research Institute on blend uniformity." We are curious as to why this guidance would be proposed before this research is complete. In addition, the Agency has not addressed the laboratory testing costs associated with performing routine blend uniformity testing.

Our experience has been that blend uniformity does not correlate to content uniformity. Our products, for which extensive content uniformity and blend uniformity results are available, were reviewed to determine the correlation coefficient between blend uniformity and content uniformity (means). The results ranging from -0.165 to 0.396 clearly support the statement that

99D-2635 C21

Chestnut Run Plaza • Centre Road • Wilmington, DE 19805 • (302) 992-3011

there is no correlation between in-process blend uniformity results and content uniformity tested at release. This is confirmed in the literature by Murray, et.al. Where his testing resulted in "the mean point label claim of the tablets was significantly different from the powder samples."

In addition to the lack of correlation between blend uniformity and content uniformity tested at release is the sampling of powder blends. The sampling of powder blends is tricky business, and a science which has not been refined. Using current technology, it is not feasible to consistently obtain representative blend samples of 1-3 times the dosage weight. In addition, multiple sampling increases the likelihood of errors in sampling. The analysis of large numbers of blend samples increases the likelihood of a random laboratory error, which cannot be invalidated in today's cGMP climate (U.S.A. vs. Barr). In addition, routine sampling of blends increases the probability of lot contamination by opening the V-blender and by use of the thief.

We believe performing blend uniformity testing at any time is inappropriate because blend uniformity testing cannot, in principle, be validated:

- The objective of the measurement is not defined. Taking samples in different locations suggests that the objective is to measure gross regional effects, while the requirement that the sample mass be commensurate with the dosage unit suggests that the objective is to measure micro-variation. Because these types of variation are completely unrelated, there is no basis in principle to assert what a given blend sampling procedure purports to measure.

- There is no objective basis to determine whether or not the measurement is measured correctly. There are many variations on how blend samples can be collected, and there is every reason to believe that different sampling methods can yield different estimates of uniformity. Basically, micro-variation often occurs as planes of segregation, and as the sample geometry is contrived to transect these planes, the observed "uniformity" can be made artificially high.

Because of the fundamentally uncertain objective of the measurement, when two sampling methodologies yield different results, there is no basis, practical or theoretical, for preferring one result over the other. We can foresee two manufacturers with identical procedures, where one has "unacceptable" uniformity result and the other routinely has acceptable results. We believe that such a situation will create perverse incentives.

We do not believe that any current required tests are similarly unverifiable.

It cannot be argued that a given sampling method is more valid because it predicts the final product uniformity without admitting that blend uniformity sampling is an inaccurate surrogate for finished-product measurements.

In the absence of a clearly defined purpose and, consequently, an inability to verify results, blend uniformity testing cannot in principle meet the minimum GMP standards for validation.

As recently as June, 1998, the FDA has removed the requirement of blend uniformity testing from individual applications based upon a "collection of sufficient data." For one particular application, these data consisted of results of 12 lots of data from four different strengths of product (three lots per strength). These data were sufficient to convince the reviewer that blend uniformity testing was not necessary for the process in question. If we believe in validation and we believe in content uniformity, why do we need to perform blend uniformity analysis for every batch? Performing blend uniformity analysis on every batch is in essence revalidating every lot. If nothing is changed in the process after process validation, why is this needed? This test adds no value to the product and significantly increases the probability of failing good batches due to laboratory error (a Type I or alpha error), increasing expenses both in testing costs and Type I failure costs.

Since it is the finished product rather than blends or other in-process materials that are administered to patients, we believe that content uniformity testing of the finished dosage form, in-process manufacturing controls, and process validation all ensure that batches produced meet product standards. In addition, extensive finished product testing during process validation studies evaluates the effect additional processing steps have on the blend. For example, it is well-documented in the literature that the transfer of the blend to the hopper and feed chutes on compression equipment results in additional mixing. Guentensberger, et al, noted this and contrasted it to the scenario presented in FDA validation guidances where it is hypothesized that disorder increases as the process progresses resulting in the necessity of blend test specifications that are tighter than finished product testing specifications.

The August, 1999, draft guidance on ANDA Blend Uniformity Analysis should be withdrawn until the FDA can demonstrate, with scientific evidence, that the implementation of routine blend uniformity testing will improve drug product quality. Section I of the draft document so notes the need for the Product Quality Research Institute to perform such studies. Why was this research not completed before implementing this requirement? In addition, FDA should no longer withhold approval of sNDA's providing for removal of routine blend uniformity assay testing pending finalization of this guidance. If sufficient data are provided to support removal of this requirement, SNDA approval should be granted.

We have the following comments:

1. Are blend uniformity analysis results expected to be reviewed prior to compression of the batch? If so, this would:
   a. not only increase QC laboratory testing, but would also necessitate a quarantine storage area prior to compression;
   b. increase cycle time due to holding of the blend in bulk;
   c. possibly lead to additional segregation of the held batch;
   d. add concerns of physical and chemical stability during the holding time.

2. We do not know how the specification 90.0-110.0%, RSD of 5% was derived. Also, what is the rationale for tighter than the USP Content Uniformity specifications, without any provisions for two-stage testing?

3. If a product's content uniformity specifications are tighter than 85.0 to 115.0%, would the Blend Uniformity Analysis specifications be tighter than those listed?

4. The first full paragraph on Page 3 begins with the sentence "Under current good manufacturing practices, (cGMPs), an applicant is required to perform a test or examination on each commercial batch of all products to monitor the output and validate the performance of processes that could be responsible for causing variability, which included adequacy of mixing to ensure uniformity and homogeneity (21 CFR 211.110(a)(3))." It should be noted that 21 CFR 211.110 (a) ends with the phrase "where appropriate." Once the process is validated, blend uniformity analysis testing is no longer "appropriate." In addition, content uniformity is performed not only to confirm adequacy of mixing to assure uniformity and homogeneity, but also to confirm the tableting process has not introduced additional variability (31 CFR 211.110(a)(3). Requiring blend uniformity analysis testing on all batches is a "leap of logic" and is not performed today by companies. Therefore, how can this practice be considered "current" for the majority of products on the market? Conversely, as 21 CFR 211.160(b) requires that "laboratory controls shall include the establishment of scientifically sound... sampling plans... designed to assure that... drug products conform to appropriate standards of identify, strength, quality and purity." Paragraph (1) requires that samples "be representative and adequately identified." How can this be accomplished when sampling a blend?

5. Page 3, "SAMPLING SIZE AND PROCEDURES": Paragraphs one and three list different sample sizes. We suggest deleting the last sentence at the end of the third paragraph, or adding "(1-3 units)" after "equivalent" in paragraphs three and four.

6. The last sentence on page four "Additional levels of testing through the use of two-tier acceptance criteria are also not recommended" obviates the need for content uniformity testing. Is this desired when content uniformity testing is performed on the actual product ingested by patient? Two-tier or "two-stage" sampling is an application of accepted statistical sampling theory - double sampling. If the first sample in double sampling does not meet specified criteria, a second sample is taken. The accept/reject decision is then based on the results of both samples with wider limits (Mil Std 414 "Sampling Plans for Variables Sampling Inspection").

We appreciate the opportunity to comment of this draft guidance.

Sincerely,

DuPont Pharmaceuticals Company

SPM22

FedEx USA Airbill

FedEx Tracking Number 806958868064

Form I.D. No. 0210

Recipient's Copy

1 From

Date 10/27/99

Sender's Name Jamie Warner Phone (302) 992-5267

Company DUPONT PHARMACEUTICAL CO

Address 974 CENTRE RD Regulatory Affairs, MR-2111 (Dept./Floor/Suite/Room)

City WILMINGTON State DE ZIP 19805

2 Your Internal Billing Reference Information

3 To

Recipient's Name Food and Drug Administration Phone ( )

Company Dockets Management Branch (HFA-305)

Address 5630 Fishers Lane, Room 1061 (To "HOLD" at FedEx location, print FedEx address here) Dept./Floor/Suite/Room

☐ Check here if residence (Extra charge applies for FedEx Express Saver)

City Rockville State MD ZIP 20852

For HOLD at FedEx Location check here

☐ Hold Weekday (Not available with FedEx First Overnight)
☐ Hold Saturday (Not available at all locations) (Available for FedEx Priority Overnight and FedEx 2Day only)

For WEEKEND Delivery check here (Extra Charge. Not available at all locations)

☐ Saturday Delivery (Available for FedEx Priority Overnight and FedEx 2Day only)
☐ NEW Sunday Delivery (Available for FedEx Priority Overnight only)

806958868064

4a Express Package Service *Packages under 150 lbs.* Delivery commitment may be later in some areas

XXXX ☒ FedEx Priority Overnight (Next business morning)
☐ FedEx Standard Overnight (Next business afternoon)
☐ FedEx First Overnight (Earliest next business morning delivery to select locations) **(Higher rates apply)**
☐ FedEx 2Day (Second business day)
☐ FedEx Express Saver (Third business day)
FedEx Letter Rate not available. Minimum charge: One pound rate.

4b Express Freight Service *Packages over 150 lbs.* Delivery commitment may be later in some areas.

☐ FedEx Overnight Freight (Next business day)
☐ FedEx 2Day Freight (Second business day)
☐ FedEx Express Saver Freight (Up to 3 business days)

(Call for delivery schedule. See back for detailed descriptions of freight services.)

5 Packaging

XXX ☒ FedEx Letter ☐ FedEx Pak ☐ FedEx Box ☐ FedEx Tube ☐ Other Pkg.
Declared value limit $500

6 Special Handling (One box must be checked)

Does this shipment contain dangerous goods?* XX ☒ No ☐ Yes (As per attached Shipper's Declaration) ☐ Yes (Shipper's Declaration not required)

☐ Dry Ice Dry Ice, 9, UN 1845 ____ x ____ kg.
☐ Cargo Aircraft Only

*Dangerous Goods cannot be shipped in FedEx packaging.

7 Payment ☐ Obtain Recipient FedEx Account No.

Bill to: XXX ☒ Sender (Account No. in Section 1 will be billed) ☐ Recipient ☐ Third Party ☐ Credit Card ☐ Cash/Check
(Enter FedEx Account No. or Credit Card No. below)

Total Packages	Total Weight	Total Declared Value	Total Charges
	XXlbs.	$ 1,00 .00	$

* When declaring a value higher than $100 per shipment, you pay an additional charge. See **SERVICE CONDITIONS, DECLARED VALUE, AND LIMIT OF LIABILITY** section for further information.

Credit Card Auth.

8 Release Signature

Your signature authorizes Federal Express to deliver this shipment without obtaining a signature and agrees to indemnify and hold harmless Federal Express from any resulting claims.

321

Questions?
Call 1·800·Go·FedEx® (800)463-3339

006067482 5

WCSL 0598
Rev. Date 3/98
Part #153023
©1994-98 FedEx
PRINTED IN U.S.A.